REMARKS

At the outset, applicants contest the propriety of making this rejection "Final" in view of applicants' amendment presented in the Response filed on June 30, 2003. For example, the amendments to claims 1 and 48, wherein tiotropium and oxitropium are specifically recited, present subject matter similar in scope to originally presented, and examined, claims 5 and 7. Claims 5 and 7 relate, respectively, to salt forms generally, and tiotropium bromide and oxitropium bromide, specifically. Thus, the amendment of claims 1 and 48 presented no subject matter requiring an additional search beyond that required in the first action to examine pending claims 5 and 7 and, thus, did not necessitate a new ground of rejection (MPEP §706.07). If the Examiner disagrees, applicants would appreciate knowing what subject matter added by amendment necessitated a new ground of rejection. Cooperation in this matter is earnestly solicited.

Accordingly, the "finality" of the rejection is believed to be premature, and the currently pending claims should be examined on the merits.

In the Office Action, claims 1, 5-9, 12-18, 21-22, 45 and 48-50 stand "rejected under 35 U.S.C. §103(a) as being unpatentable over Reiss et al. (2002/0052312 A1) in view of Meissner et al. (2002/0115680 A1)". In particular, it is alleged to

> "have been obvious to a person of ordinary skill in the art at the time the invention was made, given the general teachings of Reiss on method of treating COPD by administering a combined therapy of anticholinergics such as tiotropium bromide and a dopamine agonist to have looked in the art for specific dopamine agonists suitable for combination with anticholinergics, a[s] taught by Meissner, with the reasonable expectation of successfully preparing an effective combination therapy specific for a disorder".

Applicants respectfully traverse that rejection.

Applicants' invention relates to novel pharmaceutical compositions based on anticholinergics and dopamine agonists in the treatment of respiratory diseases. In particular, the claimed invention recites a pharmaceutical composition comprising one or

more anticholinergics selected from tiotropium and oxitropium (optionally in the form of the enantiomers, mixtures of the enantiomers or in the form of racemates thereof, and each optionally in the form of solvates or hydrates thereof) with one or more dopamine agonists. Applicants discovered, unexpectedly, that such compositions exert a synergistic effect when administered to treat inflammatory or obstructive diseases of the respiratory tract.

Reiss et al. refers to a method for treating COPD with a composition comprising muscarinic M3 receptor agonists agents such as the quarternary ammonium compounds ipratropium bromide, oxitropium bromide and tiotropium bromide and at least one therapeutic agent selected from $\beta 2$ agonists, antitussive, corticosteroid, decongestant, histamine H1 antagonist, dopamine **antagonist**, leukotriene antagonist, 5-lipooxygenese inhibitor, phosphodiesterase IV inhibitor, VLA-4 antagonist, and theophylline. Although Reiss et al. refers to the desirability of combining a muscarinic M3 receptor antagonist with another active agent, in whatever of the many combinations available according to Reiss et al., none of the combinations are directed at the use of a dopamine **agonist**, such as pramipexole or talipexole, let alone the administration of such combinations by inhalation.

Meissner et al. refers generally to the use of new anticholinergic compounds to treat COPD and asthma. Meissner et al. does not refer specifically to the combination of tiotropium or oxitropium with dopamine agonists or to the synergistic therapeutic effect produced by administration thereof. Furthermore, given the inherent variability of the activity of individual chemicals when placed in a biological environment, it is impossible to predict the effect of the claimed combination (e. g., whether mutually inhibitory or not) from Meissner, et al.

Thus, there is no dopamine agonist nexus to suggest combining Reiss et al. with Meissner et al. Accordingly, the rejection of claims 1, 5-9, 12-18, 21-22, 45 and 48-50 as

obvious over the combined teachings of Reiss et al. in view of Meissner et al. should be reconsidered and withdrawn.

Claims 19-20 stand "rejected under 35 U.S.C.§103(a) as being unpatentable over the combined references [as applied above], and further in view of Schmelzer et al (2002/0193392 A1)". Though conceding the absence of any disclosure in Reiss et al. or Meissner et al. regarding preferred particle size, with the addition of Schmelzer et al., it is alleged to

> "have been obvious to a person of ordinary skill in the art at the time the invention was made to have modified the teachings of the combined references on compositions and method of treating respiratory disorders by administering a combined active agent formulation via inhalation by implementing the preferred particle size as taught by Schmelzer because of successfully preparing a formulation that would reach the desired site".

Applicants respectfully traverse that rejection.

Schmelzer et al. refers to a pharmaceutical composition comprising tiotropium salt and a salmeterol salt in which "the adjuvants have a maximum mean particle size of up to 250μm..." [0028]. Neither Schmelzer nor Reiss et al. mention anything about combinations with dopamine agonists. Furthermore, all of the arguments (supra) made for the primary references can be applied against and overcome this rejection.

Accordingly, the rejection of claims 19-20 as obvious over Reiss et al., Meissner et al., in further view of Schmelzer et al. should be reconsidered and withdrawn.

In light of the foregoing remarks and amendments, early and favorable treatment on the merits is earnestly solicited.

Respectfully submitted,

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